CLAIMS

1. A method for enhancing the transmembrane flux rate of a permeant into a selected site of an organism comprising the steps of enhancing the permeability of said selected site of the organism to said permeant by means of

(a) porating a biological membrane at said selected site by means that form a micropore in said biological membrane, thereby reducing the barrier properties of said biological membrane to the flux of said permeant; and

(b) contacting the porated selected site with a composition comprising an effective amount of said permeant, whereby the transmembrane flux rate of said permeant into the organism is enhanced.

2. The method of Claim 1 further comprising applying to said site of said organism an enhancer to increase the flux of said permeant into said organism.

3. The method of claim 2 wherein said enhancer comprises sonic energy.

4. The method of claim 3 wherein said sonic energy is applied to said site at a frequency in the range of about 10Hz to 1000 MHz, wherein said sonic energy is modulated by means of a member selected from the group consisting of frequency modulation, amplitude modulation, phase modulation, and combinations thereof.

5. The method of Claim 2 wherein said enhancer comprises an electromagnetic field.

6. The method of Claim 5 wherein the electromagnetic field comprises iontophoresis.

7. The method of Claim 5 wherein the electromagnetic field comprises a magnetic field.

8. The method of claim 2 wherein said enhancer comprises a mechanical force.

9 The method of claim 2 wherein said enhancer comprises chemical enhancers.

10. The method of claim 2 wherein any of the methods of claims 3, 4, 5, 6, 7, 8, or 9 may be applied in any combination thereof to increase the transmembrane flux rate of said permeant into or through said micropore.

11. The method of claim 2, wherein said enhancers at said site are applied so as to increase the flux rate of the permeant into tissues surrounding the micropore.

12. The method of claim 11, wherein said enhancer comprises sonic energy.

13. The method of claim 12 wherein said sonic energy is applied to said site at a frequency in the range of about 10Hz to 1000 MHz, wherein said sonic energy is modulated by means of a member selected from the group consisting of frequency modulation, amplitude modulation, phase modulation, and combinations thereof.

14. The method of claim 11, wherein said enhancer comprises electroporation.

15. The method of claim 11, wherein said enhancer comprises iontophoresis.

16. The method of claim 11, wherein said enhancer comprises chemical enhancers.

17. The method of claim 11, wherein said enhancer comprises a mechanical force.

18. The method of claim 11 wherein said enhancer comprises a magnetic field.

19. The method of claim 11, wherein said enhancer comprises any combination thereof of the methods of claims 12, 13, 14, 15, 16, 17, and 18.

20. The method of claim 10 further comprising the method of claim 19.

21. The method of Claim 1 wherein said porating of said biological membrane in said site is accomplished by means selected from the group consisting of (a) ablating the biological membrane by contacting said site of said biological membrane with a heat source such that a micropore is formed in said biological membrane at said site; (b) puncturing said biological membrane with a micro-lancet calibrated to form a micropore; (c) ablating the biological membrane by a beam of sonic energy onto said biological membrane; (d) hydraulically puncturing said biological membrane with a high pressure jet of fluid to form a micropore and (e) puncturing said biological membrane with short pulses of electricity to form a micropore

22. The method of Claim 21 wherein said porating is accomplished by contacting said site, up to about 1000 μm across, with a heat source to conductively transfer an effective amount of thermal energy to said site such that the temperature of some of the water and other vaporizable substances in said site is elevated above their vaporization point creating a micropore to a selected depth in the biological membrane at said site.

23. The method of Claim 21 wherein said porating is accomplished by contacting said site, up to about 1000 μm across, with a heat source to conductively transfer an effective amount of thermal energy to said site such that the temperature of

some of the tissue at said site is elevated to the point where thermal decomposition occurs creating a micropore to a selected depth in the biological membrane at said site.

24. The method of claim 21 comprising treating at least said site with an effective amount of a substance that exhibits sufficient absorption over the emission range of a pulsed light source and focusing the output of a series of pulses from said pulsed light source onto said substance such that said substance is heated sufficiently to conductively transfer an effective amount of thermal energy to said biological membrane to elevate the temperature to thereby create a micropore.

25. The method of Claim 24 wherein said pulsed light source emits at a wavelength that is not significantly absorbed by said biological membrane.

26. The method of Claim 25 wherein said pulsed light source is a laser diode emitting in the range of about 630 to 1550 nm.

27. The method of Claim 25 wherein said pulsed light source is a laser diode pumped optical parametric oscillator emitting in the range of about 700 and 3000 nm.

28. The method of Claim 25 wherein said pulsed light source is a member selected from the group consisting of arc lamps, incandescent lamps, and light emitting diodes.

29. The method of claim 21 further comprising providing a sensing system for determining when the micropore in the biological membrane has reached the desired dimensions.

30. The method of claim 29 wherein said sensing system comprises light collection means for receiving light reflected from said site and focusing said reflected light on a detector for receiving said light and sending a signal to a controller wherein said signal indicates a quality of said light, and a controller coupled to said detector and to said light source for receiving said signal and for shutting off said light source when a preselected signal is received.

31. The method of claim 29 wherein said sensing system comprises an electrical impedance measuring system which can detect the changes in the impedance of the biological membrane at different depths into the organism as the micropore is formed.

32. The method of claim 21 further comprising cooling said site and adjacent tissues such that said site and adjacent tissues are in a cooled condition.

33. The method of claim 32 wherein said cooling means comprises a Peltier device.

34. The method of claim 21 further comprising, prior to porating said site , illuminating at least said site with light such that said site is sterilized.

35. The method of claim 21 comprising contacting said site with a solid element, wherein said solid element functions as a heat source to conductively transfer an effective amount of thermal energy to said biological membrane to elevate the temperature to thereby create a micropore.

36. The method of claim 35 wherein said heat source is constructed to modulate the temperature of said site to greater than 100°C within about 10 nanoseconds to 50 milliseconds and then returning the temperature of said site to approximately ambient temperature within about 1 millisecond to 50 milliseconds and wherein a cycle of raising the temperature and returning to ambient temperature is repeated one or more times effective for porating the biological membrane to the desired depth.

37. The method of claim 36 wherein said returning to approximately ambient temperature of said site is carried out by withdrawing said heat source from contact with said site.

38. The method of claim 36 wherein the modulation parameters are selected to reduce sensation to the animal subject.

39. The method of claim 31 further comprising providing means for monitoring electrical impedance between said solid element of claim 35 and said organism through said site and adjacent tissues and means for advancing the position of said solid element such that as said poration occurs with a concomitant change in impedance, said advancing means advances the solid element such that the solid element is in contact with said site during heating of the solid element, until the selected impedance is obtained.

40. The method of claim 38 further comprising means for withdrawing said solid element from contact with said site wherein said monitoring means is capable of detecting a change in impedance associated with contacting a selected layer underlying the surface of said site and sending a signal to said withdrawing means to withdrawn said solid element from contact with said site.

41. The method of claim 35 wherein said solid element is heated by delivering an electrical current through an ohmic heating element.

42. The method of claim 35 wherein said solid element is formed such that it contains an electrically conductive component and the temperature of said solid element is modulated by passing a modulated electrical current through said conductive element.

43. The method of claim 35 wherein said solid element is positioned in a modulatable magnetic field wherein energizing the magnetic field produces electrical eddy currents sufficient to heat the solid element.

44. The method of Claim 21 wherein said poration is accomplished by puncturing said site with a micro-lancet calibrated to form a micropore.

45. The method of Claim 21 wherein said poration is accomplished by a beam of sonic energy directed onto said site.

46. The method of Claim 21 wherein said poration is accomplished by hydraulically puncturing said biological membrane with a high pressure jet of fluid to form a micropore.

47. The method of Claim 21 wherein said poration is accomplished by puncturing said biological membrane with short pulses of electricity to form a micropore.

48. The method of Claim 1 wherein said permeant comprises nucleic acid.

49. The method of Claim 48 wherein said nucleic acid comprises a DNA .

50. The method of Claim 48 wherein said nucleic acid comprises RNA.

51. The method of claim 1, wherein the micropore in the biological membrane extends into a portion of the outer layer of the biological membrane ranging from 1 to 30 microns in depth.

52. The method of claim 1 , wherein the micropore in the biological membrane extends through the outer layer of the biological membrane ranging from 10 to 200 microns in depth.

53. The method of claim 1 , wherein the micropore in the biological membrane extends into the connective tissue layer of the biological membrane ranging from 100 to 5000 microns in depth

54. The method of claim 1 , wherein the micropore in the biological membrane extends through the connective tissue layer of the biological membrane ranging from 1000 to 10000 microns in depth.

55. The method of claim 1 , wherein the micropore penetrates the biological membrane to a depth determined to facilitate desired activity of the selected permeant.

56. The method of claim 1, wherein the permeant comprises a polypeptide.

57. The method of claim 56, wherein the polypeptide is a protein.

58. The method of claim 56, wherein the polypeptide comprises a peptide.

59. The method of claim 58, wherein the peptide comprises insulin.

60. The method of claim 58, wherein the peptide comprises a releasing factor.

61. The method of claim 1 , wherein the permeant comprises a carbohydrate.

62. The method of claim 61, wherein the carbohydrate comprises heparin.

63. The method of claim 1, wherein permeant comprises an analgesic.

64. The method of claim 63, wherein the analgesic comprises an opiate.

65. The method of claim 1, wherein the permeant comprises a vaccine.

66. The method of claim 1, wherein the permeant comprises a steroid.

67. The method of claim 1, wherein the permeant is associated with a carrier.

68. The method of claim 67, wherein the carrier comprises liposomes.

69. The method of claim 67, wherein the carrier comprises lipid complexes.

70. The method of claim 67, wherein the carrier comprises microparticles.

71. The method of claim 67, wherein the carrier comprises polyethylene glycol compounds.

72. The method of claim 65 combined with the method of claim 66.

73. The method of claim 1 wherein the permeant comprises a substance which has the ability to change its detectable response to a stimulus when in the proximity of an analyte present in the organism.